von Willebrand's Disease

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The preponderance of data supporting this statement is derived from:

A level 1 studies, which meet all of the evidence criteria for that study type

B level 2 studies, which meet at least one of the evidence criteria for that study type

C level 3 studies, which meet none of the evidence criteria for that study type or are derived from expert opinion, commentary or consensus

Study types and evidence criteria are defined at http://pier.acponline.org/criteria.html

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1. Prevention: Not applicable to this module.

2. Screening: Screen for VWD in specific populations only. C

2.1 Screen for VWD in women with menorrhagia and no gynecologic reason for heavy bleeding, in patients with unexplained procedural bleeding, and in individuals with a personal or family history or physical evidence of mucocutaneous bleeding. B

Specific recommendation:

- Assess for clinically significant menorrhagia:
  - Use a validated instrument patient questionnaire, such as the Pictorial Blood Loss Assessment Chart, to determine clinically significant menorrhagia
  - Note that chronic iron deficiency or chronic iron replacement therapy due to menstrual blood loss may be indicative of abnormal bleeding
- Screen for bleeding disorders in women with clinically significant menorrhagia and with a negative gynecologic evaluation.
- Screen patients with a strong history of mucocutaneous bleeing for VWD.
- Conduct a first-line coagulation screening work-up, including PT, PTT, CBC/platelets, and thrombin time.
- Recognize that initial tests for the diagnosis or exclusion of VWD include VWF function, VWF:RCo, VWF:Ag, and factor VIII activity and should be done more than once.

Rationale:

- Diagnosis is important in developing prophylaxis strategies to prevent bleeding associated with trauma, invasive procedures, or surgeries.
- Diagnosis of VWD allows for appropriate, cost-effective approaches to the management of menorrhagia and may prevent unnecessary hysterectomy.
- Because VWD is a genetic disease, detection and typing is important information for other family members.
- PT and thrombin time are normal in patients with VWD.

Evidence:

- Studies have shown that 8% of premenopausal women will seek gynecologic care for menorrhagia. As many as 50% of those with menorrhagia will be labeled as having “dysfunctional uterine bleeding” without undergoing evaluation for a bleeding disorder, and of those women, as many as 30% have an underlying bleeding disorder, and 13% have VWD (1; 2; 3; 4).
- A survey instrument known as the Pictorial Blood Assessment Chart has been developed to assess menstrual blood loses and has shown 85% sensitivity and 89% specificity in the detection of menorrhagia (blood loss >80 mL/cycle) (5).
- A CDC survey

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(http://www.cdc.gov/ncbddd/hbd/documents/UDCreport5_1.pdf) of women with type 1 VWD found that there was an average of 16 years from onset of symptoms to the diagnosis of VWD (6).
- The ACOG committee on gynecologic practice recommends screening women with menorrhagia and dysfunctional uterine bleeding for inherited and acquired disorders of coagulation (7).
- Guidelines on the diagnosis and management of VWD have been published by the UK Haemophilia Centre Doctors' Organization (8; 9) and the NHLBI (10).

Comments:
- Menorrhagia has a negative effect on quality of life and can result in chronic iron deficiency anemia, unnecessary surgeries and procedures (including hysterectomy and loss of childbearing potential), loss of school or work days, and fear of leaving home during menses.
- A recent study has shown that the diagnosis of a bleeding disorder is rarely considered by many primary physicians who are evaluating a patient for menorrhagia (1), possibly accounting for the delay in diagnosis.

3. Diagnosis: Base the diagnosis of VWD on history of bleeding, family history of a bleeding disorder, and low levels of VWF. B

3.1 Obtain a thorough history with particular emphasis on personal history of bleeding and family history of a bleeding disorder. B

Specific recommendation:
- Ask about:
  - Mucocutaneous bleeding:
    - Increased tendency for frequent or prolonged nosebleeds
    - Prolonged bleeding from lips, tongue, or frenulum after trauma
    - Bleeding with secondary dentition
    - Excessive bleeding with tooth extraction
    - Excessive bleeding with tonsillectomy
    - Menorrhagia
    - Easy bruisability, especially “spontaneous” or truncal bruising, and large or deeply colored bruises resulting from mild trauma
    - Excessive postoperative bleeding
    - Excessive GI or GU bleeding
  - “Deep” bleeding associated with low factor VIII levels that may accompany severe types of VWD:
    - Hemarthrosis
    - Muscle hematomas
    - Abdominal or retroperitoneal bleeding
    - Intracranial bleeding
  - Anemia symptoms related to blood loss or iron deficiency:
    - History of chronic iron deficiency anemia or need for chronic iron supplementation due to heavy menses

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- Weakness
- Malaise
- Decreased exercise tolerance
- Shortness of breath
- Dizziness

- Family history of clinically significant bleeding or diagnosis of VWD; if positive, obtain records to determine subtype
- Drugs that may provoke bleeding (e.g., aspirin, NSAIDs)

- See table History and Physical Examination Elements for von Willebrand's Disease.

Rationale:

- Typical signs and symptoms of bleeding as described are related to a genetic deficiency of functional VWF.
- VWF binds platelets to the subendothelium to initiate a platelet plug after an injury to the endothelium and assists in platelet-to-platelet binding; therefore, deficiency of VWF results in mucocutaneous bleeding due to poor platelet plug formation (primary hemostasis).
- VWF also binds, stabilizes, and carries factor VIII in the circulation and localizes it to the site of injury; low levels of factor VIII also contribute to bleeding risk.

Evidence:

- In a multicenter retrospective analysis of 1286 Italian patients with VWD divided by type 1, type 2, and type 3 disease, epistaxis was the most frequently reported symptom. Other symptoms reported include menorrhagia; hematomas; hematuria; bleeding after dental extraction; bleeding from wounds; gum bleeding; postoperative or postpartum bleeding; and GI, joint, or CNS bleeding (11).
- An early study of 51 members of one Swedish family found epistaxis was the most common cause of bleeding, followed by GI bleeding, bleeding from cuts and trauma, bleeding after tooth extraction, menorrhagia, and bleeding after delivery or surgery (12).
- In a survey of coagulation specialists in North America, the most common presenting complaints in patients with VWD were bleeding after dental extraction, family history of VWD, menorrhagia, and easy bruising (13).

Comments:

- VWD is the most common inherited bleeding disorder, with population-based prevalence estimates of approximately 1%, and should be considered in the differential diagnosis of patients with typical clinical signs and symptoms as described or with a suggestive family history. An epidemiologic study performed on 1218 northern Italian school children elicited a prevalence of type 1 disease as 0.82% (14). Based on the number of symptomatic patients attending hemophilia centers, prevalence estimates range from 23 to 110 per million persons (15).
- The use of bleeding scores in the diagnosis of inherited bleeding disorders has been proposed as a tool to standardize clinical assessment and diagnosis of these conditions. Further evaluation of the

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use of bleeding scores in a clinical diagnostic setting is required before their introduction into routine practice (16).

3.2 Look for signs of a bleeding disorder and anemia secondary to blood loss or iron deficiency on physical exam. C

Specific recommendation:
- Look for:
  - Multiple bruises in various stages of healing
  - Large or deeply colored purpura in response to mild trauma
  - Truncal bruising
  - Unprovoked bruising
  - Gum bleeding
  - Pallor of skin, mucus membranes, and conjunctiva
  - Tachycardia
  - Signs of CHF
- Physical exam may be unremarkable.
- See table History and Physical Examination Elements for von Willebrand's Disease.

Rationale:
- Patients with coagulation disorders including VWD may have signs of easy bruising, acute or chronic bleeding, or anemia.

Evidence:
- Consensus.

Comments:
- None.

3.3 Use laboratory testing to evaluate patients with suspected VWD or other bleeding disorders. B

Specific recommendation:
- Obtain a panel of initial tests to detect abnormal hemostasis:
  - PT
  - PTT
  - CBC/platelet count
  - Thrombin time
- Obtain LFTs, renal function tests, or DIC panel if clinically indicated.
- If PTT is prolonged and other initial test results are normal, suspect VWD as a possible diagnosis.
- Obtain VWF:RCo, VWF:Ag, and factor VIII:
  - If all screening test results are normal and the patient has clinical findings suggesting a bleeding disorder, especially if there is a family history of bleeding
  - If the platelet count is low without an apparent cause and the patient has other personal or family findings suggesting VWD
- Repeat the VWF:RCo, VWF:Ag, and factor VIII if all initial test results are normal and the patient has clear evidence of a bleeding disorder.
- Do not obtain VWF:RCo, VWF:Ag, and factor VIII if another bleeding

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disorder is diagnosed based on the initial screening test results.
- Note that a normal PTT does not necessarily exclude the diagnosis of VWD.
- See table Laboratory and Other Studies for von Willebrand's Disease.

Rationale:
- Initial screening tests are necessary because other bleeding disorders, including platelet function abnormalities, thrombocytopenia, mild hemophilias, symptomatic carriers of hemophilia, and other clotting factor deficiency states, can have similar signs and symptoms.
- Initial screening tests may identify previously undiagnosed liver or renal disease as the cause of hemostatic abnormalities.
- PFA-100 is frequently used as a screening test for VWD; however, there are conflicting data regarding its sensitivity and specificity for VWD.
- PTT will be prolonged only when factor VIII levels are lower than 30% to 35%, and thus may be normal in many patients with VWD.
- VWD will not result in prolongation of PT.
- VWD may be associated with normal screening tests, including bleeding time and PFA-100.
- VWF:RCo is the most useful diagnostic test and has been shown to have the greatest sensitivity in diagnosis of VWD.
- Mild cases of VWD may be difficult to diagnose, even with specific VWF:RCo testing, due to fluctuations in VWF and factor VIII levels in vivo; repeated testing may be required.

Evidence:
- A study of 24 children with VWD found that the combination of the ristocetin cofactor activity, bleeding time, and PTT successfully identified 92% of patients as abnormal. The combination of these tests detected more cases of VWD than either VWF antigen or factor VIII in combination with a bleeding time and PTT (17). In a comparison of PFA-100 to bleeding time in a group of 60 known patients with VWD, the bleeding time showed poor reproducibility and an overall sensitivity of 65.5%. The bleeding time was normal in 47% of type 1 VWD, 20% of type 2A, and 20% with acquired VWD. The PFA-100 showed a greater sensitivity and was more reproducible than the bleeding time (18).
- In a direct comparison of the PFA-100 to the bleeding time, the PFA-100 was significantly better then the bleeding time at identifying VWD. The sensitivity of the PFA-100 in diagnosing all cases of VWD ranged from 61% to 68% compared to 21% for the bleeding time. The specificity for diagnosing all cases was 84% for the PFA-100 vs. 98% for the bleeding time (19).

Comments:
- In a patient who has a clinical history of bleeding and at least one first-degree family member with a diagnosis of VWD, it may be appropriate to bypass the screening tests and test directly for the presence of VWD. If the VWD testing is equivocal or negative, proceed with the full screening evaluation.
- A low platelet count usually indicates a bleeding disorder other than

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VWD, although mild to moderate thrombocytopenia can be associated with type 2B, a relatively uncommon form of VWD (20).
- The PFA-100 is a newer screening test of platelet function in primary hemostasis. It simulates primary hemostasis by placing whole blood in a small tube coated with collagen in the presence of either epinephrine or adenosine diphosphate. The closure time is the time required to obtain a platelet plug in the tube. Elevated closure times are typically >120 seconds for ADP and >160 seconds for epinephrine. It is not yet available in all laboratories (18).
- For isolated prolongation of the PTT, a mixing study using normal plasma is indicated to evaluate for the presence of a circulating anticoagulant. If the PTT does not correct—and the patient has no bleeding symptoms—suspect a lupus-type anticoagulant, one of the most common causes of prolonged PTT.

3.4 Perform confirmatory laboratory work-up in patients with screening test results suggesting VWD; include testing for quantitative and functional levels of VWF as well as factor VIII levels. B

Specific recommendation:
- Obtain baseline laboratory studies:
  - VWF:RCo (functional VWF level)
  - VWF:Ag (quantitative VWF level)
  - Factor VIII activity assay
- For the most accurate assessment of the patient's true baseline levels:
  - Perform laboratory studies under basal conditions, not during periods of stress or while using hormones (e.g., postoperatively, during pregnancy, or while on oral contraceptives or hormone replacement therapy)
  - Perform tests at least 1 to 2 weeks following transfusion of blood or blood products
- Ensure that laboratory studies are performed by a specialty coagulation laboratory whenever possible and that blood is collected and handled by specially trained technicians.
- See table Laboratory and Other Studies for von Willebrand's Disease.

Rationale:
- Quantitative VWF (VWF:Ag) level should be tested simultaneously with the functional ristocetin cofactor (VWF:RCo) assay because similarly reduced levels of both suggest mild (type 1) or severe (type 3) quantitative forms of VWD.
- VWF:RCo levels lower than VWF:Ag levels (ratio <0.7) suggest a qualitative form of VWD (type 2), in which there may be normal or near normal circulating levels of VWF protein, but the protein has abnormal function.
- The initial assessment for the type of VWD is important in making therapeutic decisions.
- Knowing the factor VIII activity level is essential because patients with

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very low factor VIII levels (i.e., <10% to 20%) are likely to have more significant bleeding and will require correction of both factor VIII and VWF:RCo levels.
- Factor VIII levels cannot be predicted by measurement of VWF levels and must be specifically assayed in each patient.
- Spurious lab values may be due to improper collection, handling, processing, and transporting and may compound the already difficult task of interpreting laboratory data.

Evidence:
- The VWF:RCo level measures functional activity of the VWF protein and is the assay with the greatest sensitivity for diagnosis of VWD. Reduced VWF:RCo levels more readily predict a bleeding diathesis than quantitative VWF (VWF:Ag) levels. One study found that when using VWF:RCo levels to diagnose type 1 VWD, only 50% of diagnosed cases had low levels of VWF:Ag (21). Another study comparing VWF:RCo with VWF:Ag and factor VIII levels found that VWF:RCo was superior to either VWF:Ag or factor VIII levels in establishing the diagnosis of VWD (17).
- Laboratory studies should be drawn under optimal baseline conditions because VWF and factor VIII are acute phase reactants and can be falsely elevated. A study of 19 patients with acute infections had VWF:Ag mean concentrations three times higher than normal. High VWF:Ag levels also correlated with C-reactive protein (22).
- A cross-sectional analysis examined 175 women (90 control subjects and 85 patients with VWD) and found that the lowest levels of VWF and factor VIII occur during days 1 to 4 of menses (23). The importance of timing diagnostic testing with respect to the menstrual cycle is uncertain.
- Consensus recommendations from the National Committee for Clinical Laboratory Standards are available regarding the storage and transport of coagulation specimens (24).

Comments:
- The International Society on Thrombosis and Haemostasis has recommended abbreviations for von Willebrand factor and its activities: mature protein (VWF); antigen (VWF:Ag); ristocetin cofactor activity (VWF:RCo); and factor VIII binding capacity (VWF:FVIIIB) (25).
- For patients in whom there is a strong suspicion of VWD and who have normal or conflicting laboratory study results, repeated studies are warranted.
- Keep in mind that laboratories that do not regularly perform specialty coagulation tests should be used with caution.
- Whenever possible, avoid having special coagulation studies sent to distant reference laboratories. Although the laboratory itself may be reliable, inadequate quality control for processing and transportation of samples (such as inadequate freezing, or thawing during transport) may yield spurious results.
- It may be difficult to diagnose mild cases of VWD, which are generally type 1 disease. VWF:Ag may be lower in association with blood type O,

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and blacks may have elevated VWF:Ag. In a study of 123 women, blacks had significantly increased VWF:Ag levels compared to whites, and individuals with type O blood had significantly decreased VWF:Ag compared to non-O blood types (26).
- Blood type O is associated with mean VWF:Ag levels about 25% lower than other blood types. (27).
- An excellent overview of the difficulties in diagnosing clinically mild type 1 VWD discusses the relevance of abnormal VWF laboratory tests (28).
- It is well recognized that there are often difficulties in making the diagnosis of VWD, particularly in milder cases of type 1 VWD. The NHLBI expert panel recommends a VWF cutoff level of 30 IU/dL to support a definite diagnosis of VWD. However, this recommendation does not preclude a diagnosis of VWD in individuals with VWF levels of 30 to 50 IU/dL if there is clinical and/or family evidence of VWD, irrespective of ABO blood group (10).

3.5 Perform additional laboratory testing to characterize the type or subtype in patients who have confirmatory laboratory evidence of VWD. B

Specific recommendation:
- Diagnose type 3 VWD when levels of VWF:RCo and VWF:Ag are <5 IU/dL and factor VIII levels are <10 IU/dL.
- For all others, obtain the following laboratory tests to determine VWD type and subtype:
  - Electrophoresis for multimer analysis (useful in diagnosing type 2 VWD)
  - Ristocetin-induced platelet aggregation (diagnostic for type 2B but has poor sensitivity in other types of VWD)
  - Factor VIII binding assay (diagnostic for type 2N)
- See table Laboratory and Other Studies for von Willebrand's Disease.
- See table Types of von Willebrand's Disease.
- See table Expected Laboratory Results in Types of von Willebrand's Disease.

Rationale:
- VWF is a multimeric protein.
- Large multimers are more functionally active and are necessary for adequate platelet adhesion and thrombus formation.
- Smaller VWF multimers are less functionally active.
- Some VWD subtypes are characterized by a selective deficiency of high-molecular-weight multimers; electrophoresis is used for analysis of multimer size.
- “Gain of function” has been used to describe mutations of high-molecular-weight multimers that result in spontaneous binding to platelets. RIPA shows gain of function by increased platelet agglutination at low doses of ristocetin and is characteristic of type 2B.
- The factor VIII binding assay tests the binding affinity of VWF for factor VIII. The ability to bind factor VIII is decreased in patients with type 2N

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Evidence:
- Large multimers of VWF are needed for efficient thrombus formation. Platelet aggregation studies were done with different multimeric sizes of VWF. High-molecular-weight forms had significantly higher aggregation rates (29).
- There is a consensus regarding the use of VWF multimer assays to determine types of VWD (30).
- On multimer analysis by electrophoresis, types 1 and 2M have uniform decreases in all molecular sizes. Type 2A and type 2B lack intermediate- and high-molecular-weight multimers. Type 2N (Normandy) has a normal pattern, and type 3 will have no detectable VWF multimers (31).
- A case report of one family with VWD located two missense mutations linked to the expression of type 2B disease. The binding assays of the mutant proteins showed significantly increased binding to platelets at low doses of ristocetin (32).
- RIPA tests the ability of ristocetin to cause agglutination of platelets when testing the patient's platelet-rich plasma. Platelet agglutination in the presence of ristocetin will be abnormally decreased with most VWF abnormalities. However, in type 2B there is increased platelet agglutination in the presence of even low concentrations of ristocetin, which differentiates type 2B from other types of VWD. A case-control study of 20 patients with VWD (other than type 2B) in five unrelated families compared to 17 controls showed all patients had lower ristocetin-induced agglutination than controls by RIPA testing (20).
- In a validation study of the factor VIII binding assay, 17 patients confirmed to have VWD type 2N by mutation analysis had abnormal results compared to 127 patients with other types of VWD (33).

Comments:
- Increased sensitivity to ristocetin in the RIPA test is also found in patients with platelet-type pseudo-VWD. This is a rare disorder resulting from mutations in the platelet glycoprotein Ib/IX receptor complex, and the laboratory presentation is markedly similar to that of type 2B VWD. Plasma/platelet mixing studies and/or genetic studies are required to distinguish between type 2B VWD and platelet-type pseudo-VWD.

3.6 Consider the broad differential diagnosis of VWD. C

Specific recommendation:
- In evaluating patients with suspected VWD, consider other bleeding disorders, including:
  - Platelet function disorders
  - Thrombocytopenia
  - Hemophilias, other clotting factor deficiencies or clotting factor inhibitors
- Use clinical evaluation and logical use of hematologic tests to define the disorder, as outlined in the discussion about obtaining a thorough history.

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• See table Differential Diagnosis of von Willebrand's Disease.

Rationale:
• Accurate diagnosis is essential to appropriate management.

Evidence:
• Consensus.

Comments:
• None.

4. Consultation for Diagnosis: Consult a hematologist or a coagulation specialist if the diagnosis of VWD is suspected on the basis of initial laboratory studies. C

4.1 Consult a hematologist or a coagulation specialist, if the diagnosis of VWD is suspected, for the performance and interpretation of laboratory tests and confirmation of type or subtype. C

Specific recommendation:
• Draw initial screening laboratory studies before consulting a coagulation specialist.
• Consult a coagulation specialist for confirmation of diagnosis, type, or subtype of VWD or for retesting when screening or confirmatory laboratory studies are conflicting or nondiagnostic.

Rationale:
• An accurate diagnosis is essential but can be difficult due to the nonspecific nature of symptoms in many patients and the difficulties in obtaining accurate, reproducible laboratory data.

Evidence:
• VWF and factor VIII levels can be influenced by blood type, race, stress, and surgery and may be difficult to interpret. VWF levels are also influenced by blood type (22; 26; 27).

Comments:
• Repeated testing is necessary to diagnose mild variants of VWD.

5. Hospitalization: Hospitalize patients with VWD for control of severe bleeding and for management of potential bleeding with invasive procedures. C

5.1 Hospitalize patients with bleeding that cannot be controlled adequately in the outpatient setting. C

Specific recommendation:
• If a patient with VWD continues to have symptomatic bleeding despite outpatient or emergency room therapy, admit the patient for more aggressive therapy as well as for monitoring both the clinical and hematologic response.

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- Hospitalize a patient with VWD for major surgical or invasive procedures that require VWF replacement therapy and for monitoring of VWF and factor VIII levels.

Rationale:
- Patients who are bleeding acutely may need aggressive treatment with specific VWD therapies, including VWF-containing concentrates.
- Concentrates administered on a regular basis will require frequent clinical and laboratory monitoring.
- For major bleeding or for major surgeries, the goal is to raise both factor VIII and functional VWF to hemostatic levels and to continue treatment until initial healing has occurred or the patient is no longer at risk for bleeding.

Evidence:
- Consensus.

Comments:
- Hospitalized patients should be managed with a hematologist or coagulation specialist.

6. Non-drug Therapy: Use alternative treatment modalities in patients with VWD who do not respond to conventional drug therapy. B

6.1 Reserve non-drug therapy for selected patients. B

Specific recommendation:
- Consider non-drug therapy for the rare patient with acquired VWD due to autoantibodies against VWF or for those with congenital VWD who develop antibodies or inhibitors to VWF.
- Consider plasma exchange and extracorporeal immunoadsorption to remove circulating IgG inhibitors of VWF.

Rationale:
- VWF is rapidly cleared in patients with inhibitors, rendering ineffective standard therapies that increase plasma levels of VWF.
- Removal of antibodies may result in greater attainable levels of plasma VWF.

Evidence:
- Reviews of therapeutic options have shown that plasmapheresis and extracorporeal immunoadsorption may be effective in certain cases of acquired VWD when desmopressin and factor concentrates have short responses (36; 37).
- A patient with multiple myeloma who developed acquired VWD was successfully treated with plasma exchange (38). Results from the acquired VWD registry showed a 19% response rate in patients treated with plasmapheresis (37; 39).
- Immunoadsorption, which selectively binds IgG, facilitated removal of inhibitors in a case series that reports its effect on six patients with factor VIII inhibitors and one patient with acquired VWD (40).

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Comments:
• None.

7. Drug Therapy: Use pharmacologic and pharmacobiologic therapy to treat acute bleeding events and prevent bleeding in high-risk situations such as trauma or surgery. B

7.1 Use therapies aimed at increasing functional VWF levels in treatment of significant bleeding events or for prevention of bleeding during invasive procedures or surgeries. B

Specific recommendation:
- Use desmopressin to treat mild to moderate bleeding episodes or in preparation for minor invasive procedures or dental work:
  - Treat most mild to moderate forms of VWD with desmopressin to achieve hemostatic levels of VWF:RCo and factor VIII
  - Note that desmopressin generally is not useful for repetitive dosing because it acts by releasing stores that require several days to replete
  - Do not use desmopressin for type 2B or type 3 VWD
- Use plasma-derived concentrates of VWF and factor VIII to:
  - Raise and maintain levels of both VWF:RCo and factor VIII in the hemostatic range to treat mild to moderate bleeding in patients with type 2B and 3 VWD, or those with other types who do not respond to desmopressin
  - Treat patients who will require prolonged periods of normal hemostatic levels of VWF:RCo and factor VIII
- In patients receiving intra- and postoperative concentrates to prevent bleeding, monitor VWF:RCo and factor VIII levels whenever possible in order to adjust dosing and frequency of dosing.
- Keep in mind that the half-life of both VWF:RCo and factor VIII is approximately 12 hours so that redosing is necessary every 12 to 24 hours in patients with ongoing bleeding risks.
- See table Drug Treatment for von Willebrand's Disease.

Rationale:
- For significant or symptomatic bleeding, it is necessary to correct deficient levels of VWF:RCo and factor VIII; this is definitive therapy and can be accomplished through the recommended modalities.
- Desmopressin causes VWF to be released from storage sites into plasma, but patients with severe forms of the disease and very low baseline VWF (less than 10%) are generally poor responders to desmopressin because they lack stored VWF.
- Intermediate purity factor VIII concentrates contain VWF and are the treatment of choice for patients with VWD who respond poorly to desmopressin or who need sustained hemostatic levels of VWF and factor VIII for more than 24 to 48 hours; these products undergo viral inactivation procedures to reduce the risk of transfusion-transmitted pathogens and are considered the blood product of choice.

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- Replacement therapy allows for laboratory monitoring to ensure VWF:RCo and factor VIII levels are in the desired hemostatic range, which is important when dealing with life-threatening bleeding or ongoing surgical bleeding prophylaxis.
- In treating acute minor bleeding or in preparation for minor procedures, desmopressin is preferable in patients who are responsive to desmopressin because it avoids exposure to blood-derived products.

Evidence:

- An early study showed that desmopressin increased factor VIII coagulant activity in four patients with mild hemophilia A and two patients with VWD treated before surgery and dental extractions (41).
- Desmopressin is useful for mild to moderate bleeding in type 1 and most type 2 VWD and may be used in either its intravenous or intranasal formulation. Following diagnosis, patients should be tested for laboratory response to desmopressin. For patients who are nonresponders, significant bleeding is treated with VWF-containing concentrates derived from human plasma. This consensus information was derived from the common practices of clinicians in a North American practice survey (42).
- Desmopressin may worsen in vivo platelet aggregation leading to worsened thrombocytopenia in patients with type 2B VWD due to release of abnormal large VWF multimers with increased affinity for platelets. An in vitro study of patients with type 2B disease showed increased platelet aggregation when treated with desmopressin (43).
- Intermediate purity factor VIII concentrates are useful in treating bleeding in patients with VWD because of the presence of VWF protein in these concentrates. Several such concentrates are available in the U.S. Laboratory testing was done as part of a study to determine VWF:RCo and factor VIII levels in a variety of commercially available concentrates (44).
- Clinical response for treatment of bleeding and for surgical procedures has been shown with commercially available concentrates (45; 46).

Comments:

- VWF:RCo levels are used to monitor efficacy of desmopressin or VWF replacement therapy. Most currently available VWF-containing concentrates used for replacement therapy have potency labels in VWF:RCo units to allow for calculation of replacement doses. For example, in a patient with a baseline VWF:RCo level of 15%, a replacement dose of concentrate can be calculated in VWF:RCo units in order to bring the patient's level of VWF:RCo up to 100%.
- Patients should be tested at the time of diagnosis to determine their response to desmopressin. Responses are reproducible and allow the clinician to predict VWF:RCo and factor VIII levels after desmopressin use in an acute treatment situation.
- Desmopressin should not be used in cases of type 3 or type 2B. In type 3 VWD, there is a complete absence of VWF and no stored VWF to release. In type 2B VWD, worsening thrombocytopenia may occur.
- Factor concentrate is expensive and many hospitals do not routinely

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stock VWF-containing concentrates. Hospitals that do stock these concentrates may do so in the pharmacy or in the blood bank.
- Cryoprecipitate is no longer considered a first-line agent because of poor predictability of VWF and factor VIII levels in the product as well as the potential for transfusion-transmitted pathogens. Cryoprecipitates do not undergo the specific viral inactivation procedures used in the manufacture of factor concentrates. In an emergency situation where concentrates are not available, cryoprecipitate may be used to raise VWF:RCo and factor VIII levels.

7.2 Use therapeutic modalities that augment hemostasis through means other than by correcting or replacing VWF and factor VIII levels in special circumstances. C

Specific recommendation:
- Use antifibrinolytic agents, such as epsilon-aminocaproic acid or tranexamic acid:
  - To treat less severe forms of mucosal bleeding
  - In conjunction with desmopressin- and VWF-containing concentrates for minor and major surgery
- Use fibrin glue to promote local hemostasis.
- Consider estrogen-containing oral contraceptive pills in women with severe menorrhagia.
- See table Drug Treatment for von Willebrand's Disease.

Rationale:
- Antifibrinolytics work by stabilizing fibrin clots and are most effective in oral bleeding.
- Oral contraceptives that contain estrogen and progesterone can reduce the severity of menorrhagia in women with VWD.

Evidence:
- In one study, four women with VWD and menorrhagia were successfully treated with a single daily dose of tranexamic acid during menses (47).
- In a consensus statement, the use of fibrin glue to help control local hemostasis was listed as a treatment option in a review of diagnosis and treatment of VWD (48).
- A retrospective review of 63 patients with VWD showed that the addition of fibrin glue and antifibrinolytic therapy were effective in achieving local hemostasis in 84% of cases (49).
- In a study of 44 women with VWD, 88% found oral contraceptives to be clinically effective in the treatment of chronic menorrhagia (50).
- In a survey of women with bleeding disorders that included type 1 VWD, 50% of those with menorrhagia reported that hormonal therapy effectively reduced menses (51).

Comments:
- Besides treating the underlying VWD, treatment of secondary disorders such as symptomatic anemia and iron deficiency must also be done. Erythrocyte transfusions and iron therapy should be used if indicated.

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7.3 Use dosing guidelines to achieve adequate circulating VWF and factor VIII in commonly encountered bleeding situations. B

Specific recommendation:

- For minor bleed:
  - Raise plasma VWF:RCo and factor VIII levels above 30% to 50%
- For major bleed:
  - Raise plasma VWF:RCo and factor VIII level above 50%
- For life-threatening bleed or major head trauma:
  - Raise plasma VWF:RCo and factor VIII to 100%
- For minor surgery:
  - Raise and maintain plasma levels of VWF:RCo and factor VIII levels above 50% until the procedure is complete; with minor procedures a single treatment of desmopressin or factor concentrate may be sufficient
- For major surgery:
  - Raise and maintain plasma levels of VWF:RCo and factor VIII above 50% until initial healing is complete, followed by gradual tapering of the concentrate dose, depending on postoperative activity levels
- For dental work especially those requiring deep nerve blocks:
  - Raise plasma level of VWF:RCo and factor VIII levels to more than 30% to 50% for at least 12 hours, followed by daily oral antifibrinolytic agents for 7 to 10 days
- For significant menorrhagia, choose among several options to achieve clinical benefit:
  - Desmopressin at beginning of menses
  - Antifibrinolytic therapy at the beginning or throughout menses
  - Hormonal therapy for persistent menorrhagia
- For patients with severe VWD and frequent bleeding episodes, particularly in patients with severe type 3 VWD, regular prophylactic dosing of VWF-containing concentrates may be used to prevent bleeding.
- See table Drug Treatment for von Willebrand's Disease.

Rationale:

- Various types of bleeding require different approaches to achieve hemostatic levels of VWF and factor VIII.
- Duration of treatment depends on the ongoing risk of bleeding or rebleeding and must be assessed for each clinical situation.
- On average, VWF:RCo at a dose of 50 IU/kg will raise the plasma level of VWF by 100% (or 1 IU VWF/mL plasma).

Evidence:

- Specific recommendations were adapted from a review paper for treatment of scenarios including major surgery, minor surgery, dental extractions, and spontaneous bleeding episodes (48).
- General recommendations regarding desmopressin, antifibrinolytic therapy, and hormonal therapy for treatment of menorrhagia were developed based on multicenter experience (52).

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Comments:
- Alloantibodies may develop in patients with type 3 VWD with repetitive use of factor concentrates, leading to poor responsiveness to therapy. If factor replacement therapy loses its efficacy, consult a coagulation specialist immediately for specialized testing and management.

8. Patient Education: Inform patients with VWD about the prognosis and overall management of the disease. C

8.1 Educate patients and their families about VWD and the management of bleeding. C

Specific recommendation:
- Inform patients with known VWD of their increased risk of bleeding, basing risk assessment on disease type and severity.
- Educate patients about different treatment options appropriate for their type of VWD and review possible side effects and risks.
- Discuss with patients the signs and symptoms of bleeding and instruct them to seek medical care if uncontrolled bleeding occurs.
- Discuss the management of minor bleeding or menorrhagia at home using therapeutic options such as desmopressin, antifibrinolytic drugs, or factor concentrates.
- Inform patients about high-risk situations for which prophylaxis may be recommended, such as invasive procedures, dental work, and trauma.
- Advise patients about risks associated with trauma and precautions for head trauma:
  - For severe forms of VWD, concentrate therapy and CT scanning may be recommended for head trauma
  - For less severe forms of VWD, evaluation with CT scanning along with therapy with desmopressin or concentrates may be recommended
- Reassure patients that although they are at an increased risk of bleeding, there is no evidence that life expectancy is shortened.
- Advise patients with VWD to inform all of their treating physicians about their underlying condition.
- Counsel patients with VWD that family members should be screened for the disease when medically indicated.
- Instruct patients with severe forms of VWD and frequent bleeding episodes about home infusion of factor concentrates.

Rationale:
- Patients can avoid emergency care for minor or moderate bleeding episodes if education for self-administration of home therapy is provided.

Evidence:
- Home therapy has proven to be effective. A prospective study of home-based treatment using intranasal desmopressin was performed in 100 patients with mild to moderate VWD and 69 with mild hemophilia A. Desmopressin was effective in controlling bleeding in 85% of cases (56).

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Comments:
- Use resources available through the nearest federally designated hemophilia treatment center.

9. Management Consultation: Consult a hematologist or coagulation specialist if available for help in managing complications and potential complications of VWD. C

9.1 Consult a coagulation specialist for management of serious bleeding, trauma, or surgical procedures. C

Specific recommendation:
- Consult a coagulation specialist for management of life-threatening bleed or major surgery that requires hospitalization.
- Consult a coagulation specialist for help in management of a patient during pregnancy and delivery.
- Refer patients with VWD to the nearest federally designated comprehensive hemophilia treatment center whenever possible.

Rationale:
- Bleeding in VWD must be managed with good planning, availability of needed therapies, and access to onsite laboratory monitoring; a comprehensive team approach is advisable.
- Treatment for major bleeding episodes or surgery is complex and costly.
- Physicians who specialize in the care of patients with bleeding disorders have the knowledge and experience necessary to deliver cost-effective, state-of-the-art care and generally utilize a team of professionals trained in comprehensive care.

Evidence:
- Mainly consensus.
- Recommendations from the Association of Hemophilia Clinic Directors of Canada suggest that consultation should be obtained for dental and surgical care of patients with VWD (57).

Comments:
- Treatment with factor concentrates for bleeding or surgery is complex and costly.
- Inadequate or poorly planned treatment may result in life- and limb-threatening bleeding.

10. Follow-up Issues: Follow patients with VWD on a regular basis for assessment of bleeding problems. C

10.1 Monitor patients for changes in bleeding patterns and response to therapy. C

Specific recommendation:
- At each visit, in addition to the appropriate history and physical exam,

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review the patient's bleeding log and home treatment of bleeding.
- In patients experiencing repetitive bleeding at one site, refer for evaluation for underlying problems (for example, a patient with frequent epistaxis should be referred to an ENT physician for evaluation).
- For bleeding that is not well controlled with a home therapy plan, consult the patient's coagulation specialist for further management strategies.
- Regularly review medications and advise patients to avoid aspirin-containing compounds and use NSAIDs with caution and close follow-up.
- Follow hemoglobin/hematocrit regularly.
- Replace iron as needed.
- See table Elements of Follow-up for von Willebrand's Disease.

Rationale:
- Management is focused on educating patients to recognize and treat minor bleeding in the home setting.
- Follow-up visits will assess problems related to bleeding and the patient's ability to manage bleeding symptoms at home.

Evidence:
- Consensus.

Comments:
- None.

10.2 Recommend that patients with VWD be immunized against hepatitis A and B. C

Specific recommendation:
- Check immune status to hepatitis A and hepatitis B.
- Immunize patients who are not immune.
- See table Elements of Follow-up for von Willebrand's Disease.

Rationale:
- HAV and HBV are preventable blood-borne infections, and it is a standard of care to recommend immunity to HAV and HBV for patients with bleeding disorders.

Evidence:
- Consensus.

Comments:
- None.

10.3 Closely follow women with VWD who become pregnant. B

Specific recommendation:
- Consult a hematologist or the patient's hemophilia treatment center for peripartal management.
- Obtain factor VIII and VWF:RCo levels near 36 weeks gestation.
- For levels of factor VIII or VWF:RCo less than 50%, treat to raise levels to more than 50% before anesthesia and delivery; treatment is usually with replacement VWF-containing concentrates before delivery.

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- For vaginal deliveries, continue treatment to maintain hemostatic factor levels until bleeding risk is decreased; treatment duration depends on baseline levels, thus patients with severe deficiencies may need treatment for longer durations.
- Be aware that for caesarean sections, treatment guidelines and treatment duration will be the same as for major surgery (see information on therapeutic modalities that augment hemostasis).
- Recognize that for patients with hemostatic levels of factor VIII and VWF at 36 weeks gestation, no therapy is needed at delivery; however, reconfirm levels 3 to 5 days after delivery:
  - For persistent bleeding, raise levels as needed after delivery with desmopressin or VWF-containing concentrates, depending on the patient's baseline levels and responsiveness to desmopressin
- Avoid vacuum extraction and fetal scalp electrodes.
- See table Elements of Follow-up for von Willebrand's Disease.

Rationale:
- Factor VIII and VWF levels rise during pregnancy (especially in the third trimester) for normal individuals and for patients with mild to moderate VWD; i.e., patients with type 1 and some with type 2 VWD.
- Measuring levels near the end of gestation will determine which patients will require treatment before delivery.
- Levels will fall toward baseline soon after delivery.
- Postpartum hemorrhage, including delayed hemorrhage, is more likely in type 3 and some type 2 subsets than in type 1 VWD.
- Desmopressin should be used with care before delivery because of possible premature labor, hyponatremia, and seizures.

Evidence:
- In a report of 24 pregnancies in 13 patients with VWD, the overall incidence of primary and secondary postpartum hemorrhage was 15.8% and 25%, respectively (58).
- In another review of 84 pregnancies in 31 women with VWD (27 with type 1 VWD), there were 18 spontaneous miscarriages and excessive postpartum bleeding in 10 of 54 deliveries (6 of 54 required blood transfusions). Secondary hemorrhage was reported in 11 of 54 deliveries. No hemorrhage occurred in 10 patients with VWD who had been given prophylactic treatment at the time of delivery (59).
- A review article discusses the diagnosis and treatement of VWD in pregnancy (60).

Comments:
- None.

10.4 Refer patients with VWD to a comprehensive center for bleeding disorders, if available, for long-term follow-up. C

Specific recommendation:
- Refer patients with VWD to the nearest federally designated comprehensive hemophilia treatment center for annual follow-up visits as well as ongoing consultations when needed.

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Rationale:

- In the U.S. there is a network of federally designated hemophilia treatment centers that provide comprehensive care for patients with congenital bleeding disorders.
- Comprehensive care includes medical treatment, patient education, rehabilitation, social services, family support, and genetics testing and counseling.

Evidence:

- Although there are no studies showing the benefit of specialty care for VWD, one recent study showed that hemophilia patients receiving care from comprehensive hemophilia treatment centers had a significantly reduced mortality rate compared to those who did not (61).
- Consensus recommendations have been provided by the Association of Hemophilia Clinic Directors of Canada. Patients should be followed at a center that offers expertise in diagnosis, assessment, and management of bleeding and complications. A center should also meet the educational and counseling needs of patients, family members, and health care providers regarding optimal use of therapy (57).

Comments:

- None.

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1 Studies that meet all of the evidence criteria for that study type

2 Studies that meet at least one of the criteria for that study type

3 Studies that meet none of the evidence criteria for that study type or are derived from expert opinion, commentary, or consensus

Study types and evidence criteria are defined at http://pier.acponline.org/criteria.html

The number in parentheses at the end of the reference citations identify PubMed abstracts, which can be found on the National Library of Medicine's web site http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

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von Willebrand's Disease

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von Willebrand's Disease

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Glossary

ADP	adenosine diphosphate
CBC	complete blood cell (count)
CHF	congestive heart failure
CNS	central nervous system
CT	computed tomography
DDAVP	1-deamino-8-D-arginine-vasopressin (desmopressin)
DIC	disseminated intravascular coagulation
ENT	ear, nose, and throat
GI	gastrointestinal
GU	genitourinary
HAV	hepatitis A virus
HBV	hepatitis B virus
IgG	immunoglobulin G
ITP	idiopathic thrombocytopenic purpura
IU	international units
iv	intravenous
LFTs	liver function tests
NSAID	nonsteroidal anti-inflammatory drug
PFA-100	platelet function analyzer
po	orally
PT	prothrombin time
PTT	partial thromboplastin time
qid	four times daily
RIPA	ristocetin-induced platelet aggregation
VWD	von Willebrand's disease
VWF	von Willebrand's factor
VWF:Ag	von Willebrand's factor:antigen
VWF:RCo	von Willebrand's factor:ristocetin cofactor

Acronyms

ACOG	American College of Obstetrics and Gynocology
CDC	Centers for Disease Control and Prevention
NHLBI	National Heart, Lung, and Blood Institute

History and Physical Examination Elements for von Willebrand's Disease

Category	Element	Notes
History	Mucocutaneous bleeding	Ask about epistaxis and menorrhagia without underlying gynecologic disorder
History	Excessive bleeding after procedures	Ask about dental extraction, tonsillectomy, or other surgical procedures
History	History or symptoms of iron deficiency	Ask about anemia and malaise, weakness, and decreased exercise tolerance, as well as abnormal bleeding
History	Family history of bleeding or diagnosis of VWD	Evaluate any patient with bleeding symptoms and a positive family history
History	Medication history	Ask about drugs that can provoke bleeding such as aspirin and NSAIDs; patients with VWD are often sensitive to the antiplatelet effect of these drugs
Physical exam	Mucocutaneous exam for pallor or signs of bleeding in conjunctiva, skin, and mucous membranes including multiple bruises, gum bleeding, purpura, and petechiae	Physical findings, if any, are related to mucocutaneous bleeding, chronic anemia from blood loss, or both

VWD = von Willebrand's disease; VWF = von Willebrand's factor.

Laboratory and Other Studies for von Willebrand's Disease

Test	Notes
PT/PTT	PT normal, PTT may be prolonged in all types if factor VIII level is low
PFA-100	May not be available
Platelet count/CBC	If acutely bleeding, may recognize need for transfusion; platelet count may be low in type 2B VWD
VWF:Ag	May be normal in type 2 disease. Will be proportionate to VWF:RCo in type 1. Will be very low in type 3. May be falsely elevated by stress, surgery, pregnancy, exercise, and exogenous estrogens
VWF:RCo	Proportionate to VWF:Ag in type 1; will be low or undetectable in type 3. Low in type 2 disease. May be falsely elevated by stress, surgery, pregnancy, exercise, and exogenous estrogens
Factor VIII	May be normal to low. Low levels contribute to bleeding diathesis
Multimer analysis	Proportionate decrease in all multimers in type 1 and 2M; absence of high-molecular-weight multimers in 2A, 2B; and absence of all multimers in type 3
RIPA	Type 2B shows increased agglutination with low-dose ristocetin; all other types show decreased agglutination with all doses of ristocetin
Factor VIII binding assay	Decreased in type 2N VWD

CBC = complete blood cell (count); PFA-100 = platelet function analyzer; PT = prothrombin time; PTT = partial thromboplastin time; RIPA = ristocetin-induced platelet aggregation; VWD = von Willebrand's disease; VWF = von Willebrand's factor; VWF:Ag = von Willebrand's factor:antigen; VWF:RCo = von Willebrand's factor:ristocetin cofactor.

Differential Diagnosis of von Willebrand's Disease

Disease	Characteristics	Notes
Platelet function disorder	Signs and symptoms include mucocutaneous bleeding, bruising, or postoperative bleeding. Laboratory studies show prolonged bleeding time, abnormal PFA-100, or both and abnormal findings on platelet aggregation studies. Normal PT, PTT, and VWF:RCo. Platelet count is usually normal	Congenital causes include Glanzmann's thrombasthenia, Bernard-Soulier syndrome, and platelet storage pool disorders. Acquired disorders may be due to chronic renal failure and drugs that inhibit platelet function
Thrombocytopenia	Signs and symptoms of mucocutaneous-type bleeding. Laboratory findings include low platelet count with a normal PT, PTT, and VWF:RCo. Elevations in bleeding time, PFA-100 are usually inversely proportional to platelet count and are not indicated	Congenital disorders include Fanconi's anemia, Wiskott-Aldrich syndrome, Alport syndrome, and thrombocytopenia with absent radii syndrome. Thrombocytopenia is more common due to an acquired disorder such as ITP, DIC, liver disease, or hypersplenism
Hemophilias	Signs and symptoms include trauma-related or spontaneous bleeding, especially into joints and soft tissue. Laboratory findings include a normal bleeding time, normal PT, prolonged PTT, and deficient factor VIII or factor IX level (<30%)	Inheritance is X-linked. Type 2N VWD should be considered when there is a low factor VIII level, normal von Willebrand's studies, and an inheritance pattern not consistent with hemophilia A. Specific testing is done with a factor VIII binding assay. See information on additional laboratory testing
Symptomatic carriers of hemophilia	Signs, symptoms, and laboratory values same as for mild hemophilia	Female carriers of hemophilia A or hemophilia B may have factor levels less than 50% with mild to moderate bleeding symptoms
Other clotting factor deficiency states such as factor XI, factor VII (and rarely factor X, factor V, or fibrinogen)	Easy bruising and easy bleeding. Laboratory findings include normal bleeding time and platelet count. Abnormal PT or PTT, depending on which factor is deficient	Autosomal inheritance; heterozygotes may be symptomatic when clotting factor levels are less than 20% to 30%
Circulating inhibitors to clotting factor VIII	Easy bruising and easy bleeding. Most commonly due to autoantibodies against factor VIII, resulting in a prolonged PTT that does not correct in a mixing study; PT, bleeding time, and platelet count are normal	Acquired. Rare disorder due to development of IgG autoantibodies against factor VIII. May be spontaneous in the elderly or associated with pregnancy, malignancy, or autoimmune disorders
Circulating inhibitors to prothrombin	Easy bruising and bleeding. Laboratory findings include a lupus anticoagulant associated with a prolonged PT	Acquired. Rare complication of lupus anticoagulants in which the antibodies have activity against prothrombin, leading to a bleeding diathesis
Low VWF levels due to extreme thrombocytosis	Spontaneous bleeding or risk of bleeding with trauma or surgeries. Laboratory studies show markedly elevated platelet count	Acquired. Rare complication of extreme thrombocytosis. Reduction of the platelet count can restore normal levels of circulating VWF (34; 35)

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; IgG = immunoglobulin G; PFA-100 = platelet function analyzer; PT = prothrombin time; PTT = partial thromboplastin time; VWD = von Willebrand's disease; VWF = von Willebrand's factor; VWF:RCo = von Willebrand's factor:ristocetin cofactor.

Drug Treatment for von Willebrand's Disease

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Desmopressin	Vasoconstrictor that causes release of VWF from endothelial stores	0.3 µg/kg iv desmopressin or 10 µg dose of intranasal desmopressin	No risk of transfusion-transmitted disease. Easily self-administered (especially intranasal Stimate®). Useful for mild to moderate bleeding, menorrhagia, prophylaxis for minor invasive procedures, and dental work	Flushing, headache, nausea, water intoxication, hyponatremia	Can be used iv over 30 min, subcutaneously or intranasally. Response to desmopressin should be determined at the time of diagnosis of VWD, before its use. Tachyphylaxis occurs with desmopressin, and use is typically limited to 1 or 2 days. Monitor sodium level and do not administer unnecessary fluids
Antihemophilic factor (human) (VWF-containing factor VIII concentrates [intermediate purity factor VIII concentrates])	Increases blood levels of VWF and factor VIII	Varies by treatment needed; 20-50 IU/kg every 12 to 24 hours to achieve and maintain hemostatic levels of VWF and factor VIII	Low risk of transfusion-transmitted pathogens due to purification and specific viral inactivation steps. Rich in VWF. Contents listed by VWF:RCo	Rare development of alloantibodies in type 3 disease (48). High cost	Intermediate-purity factor VIII concentrates rich in VWF, with ratio of VWF:RCo:factor VIII includes Humate-P®, 2.5:1; Koate-DVI®, 1.2:1; and Alphanate®, 0.5:1 (44)
Cryoprecipitate	Increases blood levels of VWF and factor VIII	Varies by treatment needed. Give q 12-24 h	Available in most settings if concentrates are not available for emergency treatment	Risk of blood-borne transmissions (53)	Rarely used secondary to other choices. Each bag contains 80-100 units of VWF
Aminocaproic acid (Amicar®)	Inhibits fibrinolysis	Initial loading dose of 5000 mg given before a procedure; then 50 mg/kg qid either po or iv for bleeding or surgical prophylaxis	No transfusion-transmission risk. Particularly useful in controlling mucocutaneous or oral bleeding	Contraindicated in bleeding of upper urinary tract because of risk of obstructive uropathy from clotting (54)	Add with dental extractions, tonsillectomy, menorrhagia, mucosal hemorrhage (Amicar®, tranexamic acid) (55) Adjunct to agents that increase VWF
Tranexamic acid (Cyklokapron®)	Inhibits fibrinolysis	20-25 mg/kg q 8-12 h po, iv, or topical	More potent than aminocaproic acid	Contraindicated in bleeding of upper urinary tract because of secondary risk of obstructive uropathy from clotting (54)	Add with dental extractions, tonsillectomy, menorrhagia, mucosal hemorrhage (Amicar®, tranexamic acid) (55) Adjunct to agents that increase VWF

Table Continued...

Drug Treatment for von Willebrand's Disease

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Estrogenic compounds	Mechanism unknown, but increases serum level of VWF and factor VIII	Variable, depending on type of preparation	May reduce menorrhagia	Headache, hypertension	Not able to predict response. May also have favorable effect on endometrium (54)
Fibrin sealant (Tisseel®)	A concentrate of fibrinogen combined with thrombin and calcium to form gelatinous fibrin-rich glue	Forms a gel for topical use	May control local bleeding. Useful in some surgeries	Risk of blood-borne disease when cryoprecipitates are used as a source of fibrinogen	May be an adjunct to other therapies in controlling bleeding
VWF concentrate	Raises VWF levels	Dose by VWF:RCo units	Highly purified plasma-derived VWF concentrate. Viral inactivation	Rare instance of development of VWF antibodies in type 3 VWD (48)	Start 12-24 hours before needed, level secondary to de novo synthesis of factor VIII. Must use in conjunction with factor VIII concentrate in an acute bleed. Not available in U.S.

iv = intravenous; IU = international units; po = orally; qid = four times daily; VWD = von Willebrand's disease; VWF = von Willebrand's factor; VWF:RCo = von Willebrand's factor:ristocetin cofactor.

Elements of Follow-up for von Willebrand's Disease

Category	Issue	How?	How Often?	Notes
History	Frequency of bleeding episodes and efficacy of treatment	Ask about bleeding episodes such as epistaxis and menorrhagia. Review patient history and bleeding log	Depends on frequency and severity of bleeding episodes	Patients should be asked to maintain a bleeding log that notes date, type of bleed, treatment used, and if concentrate is used, the lot number
History	Anemia	Ask about anemia-related symptoms such as weakness, fatigue, and shortness of breath	Depends on frequency and severity of bleeding episodes	
History	Dental problems	Ask about oral or dental problems and if the patient sees a dentist regularly	Annually	
Physical exam	Bleeding	Look for bruising. Perform musculoskeletal and range of motion exam for patients with severe disease (type 3) with joint bleeding	Depends on the frequency and severity of bleeding episodes	
Physical exam	Anemia	Look for pallor	Depends on the frequency and severity of bleeding episodes	
Laboratory	Anemia	CBC	Depends on the frequency and severity of bleeding episodes	
Drug therapy	Bleeding	Adjust medications for the control of symptoms	Only if indicated during acute bleeding or prevention of bleeding	
Patient education	Overall management	Use the comprehensive team approach provided at a hemophilia treatment center	Annually	For information on patient and family education and support issues, see referral to comprehensive centers for bleeding disorders

CBC = complete blood cell (count).

Types of von Willebrand's Disease

Type	Description	Notes
1	Mild to moderate lowering of both quantitative (VWF:Ag) and functional levels of VWF (VWF:RCo). Normal VWF functional activity relative to antigen level. VWF multimer distribution is normal—the proportion of large multimers is not significantly decreased	Most common variant (70% of all VWD) Mostly autosomal dominant Multimeric structure of the VWF protein is intact Factor VIII level may or may not be low Bleeding may be mild Median age at first bleed of 10 years and median age at diagnosis of 13 years reported from females followed at hemophilia treatment centers (6)
2	Qualitative abnormalities of the VWF protein; qualitative level (VWF:RCo) is generally lower than quantitative level (VWF:Ag, except type 2N VWD)	Represents 20%-30% of VWD Autosomal dominant or recessive Bleeding may be mild or severe Median age at first bleed of 4 years and median age at diagnosis of 7 years reported from females followed at hemophilia treatment centers (6)
Subtype 2A	Decreased production of intermediate and large multimers	Most common qualitative variant of VWD Can lead to severe mucocutaneous bleeding Selective loss of intermediate and large multimers Low VWF:RCo with normal to reduced VWF:Ag
Subtype 2B	Loss of large multimers due to spontaneous binding to platelets; increased platelet clearance and thrombocytopenia	Characterized by enhanced RIPA Selective loss of large multimers Features include mild thrombocytopenia and low to normal factor VIII

Table Continued...

Types of von Willebrand's Disease

Type	Description	Notes
Subtype 2M	Qualitatively abnormal VWF protein with preservation of multimeric structure	Increased VWF-platelet binding due to mutations that alter the VWF region responsible for platelet binding Normal multimer analysis
Subtype 2N	Decreased affinity for factor VIII. Autosomal recessive disorder. VWF platelet-dependent functions are normal	Normal levels of VWF:Ag and VWF:RCo and normal multimer analysis Low plasma factor VIII level Consider in cases diagnosed as mild hemophilia A where the inheritance pattern is unknown or inconsistent with an X-linked disorder Diagnosis confirmed by factor VIII binding assay
3	Severe quantitative deficiency of the VWF protein; loss of all multimers	Least common variant (1%-3% of all VWD) Autosomal recessive (may be homozygous or compound heterozygous for VWF mutations) Complete absence or profound deficiency of VWF and factor VIII Median age at first bleed and median age at diagnosis of 1 year reported from females followed at hemophilia treatment centers (6)
Platelet-type/pseudo	A primary platelet disorder. No abnormality in the VWF protein	Rare; probable autosomal recessive inheritance pattern Increased affinity of platelet GPIb/IX/V receptor complex for normal VWF Laboratory and clinical similarity to type 2B
Acquired	Normal VWF is rapidly removed from plasma by the presence of antibodies or abnormal binding to tumor cells	Rare, not congenital Suspect in a patient with acquired platelet type bleeding, no family history, and laboratory studies consistent with VWD Underlying disorders include lymphoproliferative disease, myeloproliferative disease, cardiovascular disease, and neoplasia

Table Continued...

RIPA = ristocetin-induced platelet aggregation; VWD = von Willebrand's disease; VWF = von Willebrand's factor; VWF:Ag = von Willebrand's factor:antigen; VWF:RCo = von Willebrand's factor:ristocetin cofactor.

Data from 62; 63; 64.

Expected Laboratory Results in Types of von Willebrand's Disease

Lab Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	Platelet-VWD
Bleeding time	Normal to ↑	Normal to ↑↑	Normal to ↑	Normal to ↑↑	Normal	↑↑↑	Normal to ↑
PFA-100	↑	↑	↑	↑	Normal	↑↑↑	↑
PTT	Normal to ↑	Normal to ↑	Normal to ↑	Normal to ↑	↑	↑↑	Normal to ↑
Platelet count	Normal	Normal	↓	Normal	Normal	Normal	↓
VWF:Ag	↓	↓	↓	Normal to ↓	Normal	↓↓↓	↓
VWF:RCo	↓	↓↓	↓↓	↓	Normal	↓↓↓	↓↓
VWF, high-molecular-weight multimer	Normal	↓↓↓	↓↓↓ (usually)	Normal	Normal	↓↓↓	↓↓
RIPA	↓ (if VWF <30 IU/dL)	↓	↑	↓	Normal	↓	↑
Factor VIII	Normal to ↓	Normal to ↓	Normal to ↓	Normal	↓↓	↓↓↓	Normal
Factor VIII binding assay	Normal	Normal	Normal	Normal	↓↓	Normal	Normal

PFA-100 = platelet function analyzer; PTT = partial thromboplastin time; RIPA = ristocetin-induced platelet aggregation; VWF = von Willebrand's factor; VWF:Ag = von Willebrand's factor:antigen; VWF:RCo = von Willebrand's factor:ristocetin cofactor.